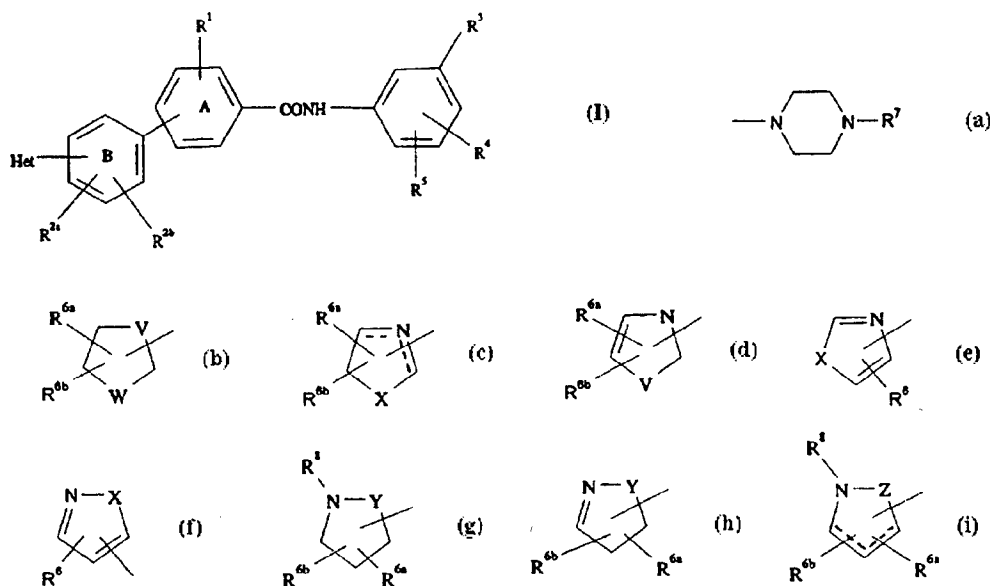




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(54) Title: BENZANILIDE DERIVATIVES AS 5-HT_{1D}-ANTAGONISTS**(57) Abstract**

Compounds of formula (I) and salts and solvates (eg hydrates) thereof, in which R¹ represents a hydrogen atom, a halogen atom, C₁-alkyl or C₁-alkoxy; R^{2a} and R^{2b} each represents H, a halogen atom, C₁-alkoxy, hydroxy or C₁-alkyl; R³ represents the group (a); R⁴ and R⁵ each represents H, a halogen atom, hydroxy, C₁-alkoxy or C₁-alkyl; Het represents a group selected from (b), (c), (d), (e), (f), (g), (h) or (i); R⁶ represents a hydrogen atom, -NR⁹R¹⁰ or C₁-alkyl optionally substituted by one or two substituents selected from C₁-alkoxy, hydroxy and -OCOR¹¹; R^{6a} and R^{6b}, each represents H hydroxy or C₁-alkyl optionally substituted by one or two of C₁-alkoxy or hydroxy; R⁷, R⁸ and R⁹ are each H or C₁-alkyl; R¹⁰ represents a hydrogen atom C₁-alkyl, COR¹¹, benzoyl or -SO₂R¹¹; R¹¹ represents C₁-alkyl or phenyl; V and W each represent oxygen or a sulphur atom; X represents an oxygen atom or the group NR⁸ or S(O)_K; where K is zero, 1 or 2; Y represents an oxygen atom or the group NR⁸ or SO₂; Z represents a sulphur atom or the group NR⁸; and --- represents a double bond in either of the positions indicated; are useful in the treatment of depression and other CNS disorders.

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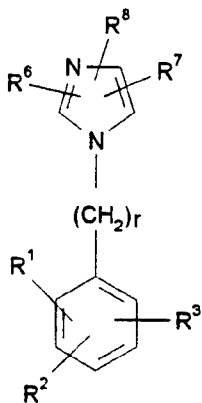
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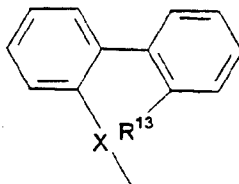
Benzanilide derivatives as 5-HT_{1D}-antagonists

This invention relates to novel benzanilide derivatives, to processes for their preparation, and to pharmaceutical compositions containing them.

European patent application no. 0253310 discloses angiotensin II antagonists of formula



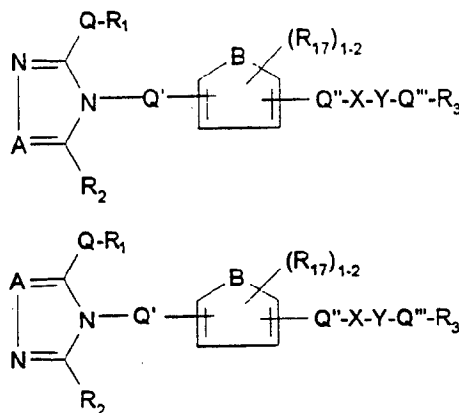
wherein R¹ is inter alia the group



where X is inter alia -CONH- and R¹³ is inter alia a substituted triazolyl group; R² and R³ each represents inter alia H, halogen C₁₋₄alkyl or C₁₋₄alkoxy; and r is zero, 1 or 2.

The compounds lack the characteristic piperazinyl substituent of the compounds of the present invention, and differ from the presently claimed compounds in their utility.

European patent application no. 0335381 discloses compounds of formulae



wherein

A is N or CH;

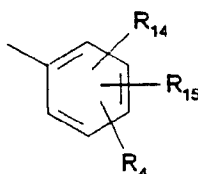
B is inter alia CH = CH;

5 Q is a single bond, C₁₋₃ alkylene, O or NR₁₆;

Q' Q'' and Q''' is each inter alia a single bond;

R₁ is an aromatic substituent;

R₃ is inter alia



10

where R₄ is inter alia a C₁₋₁₂alkyl group substituted by inter alia, an N-heterocyclic group bound to the alkyl via the cyclic nitrogen atom and capable of containing O, S or NR₁₆ as a further hetero ring member; and

15 X-Y is inter alia -CONH-.

The compounds are said to have platelet activating factor antagonist activity. There is no suggestion of compounds wherein there are two phenyl rings between the heterocyclic group and the amide linkage

20

British patent specification no. 1157586 discloses the preparation of anti-bacterial compounds of formula:

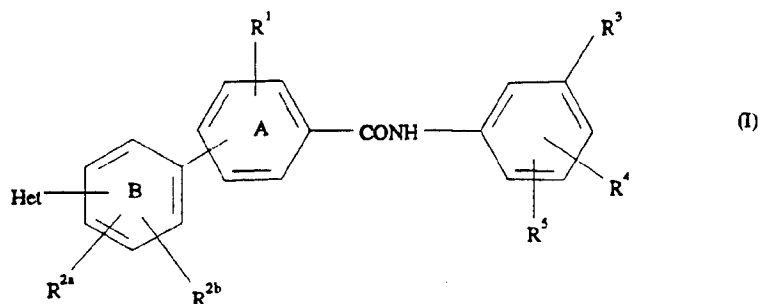


25

wherein R₂ and R₃ each represents an optionally substituted aryl group. There is

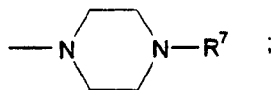
no suggestion of the particular substituted phenyl moieties of the compounds of the present invention.

According to the invention we provide compounds of the general formula (I) :-

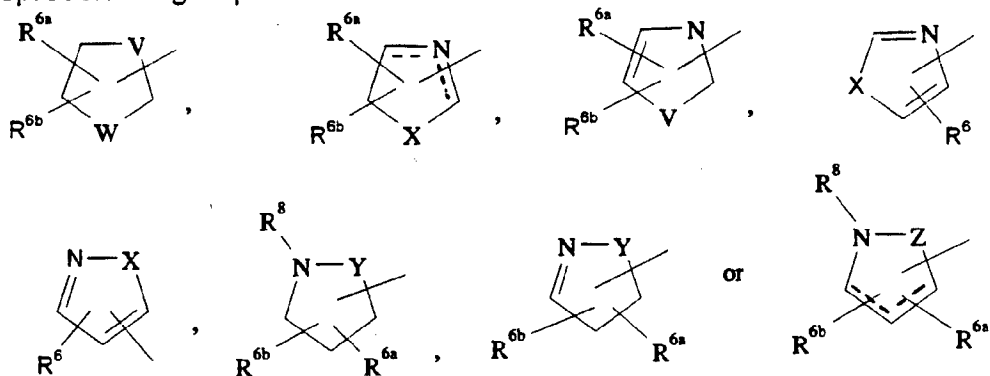


and salts and solvates (eg hydrates) thereof, in which

- 10 R^1 represents a hydrogen atom, a halogen atom, C_{1-6} alkyl or C_{1-6} alkoxy;
 R^{2a} and R^{2b} , which may be the same or different, each independently represents a hydrogen atom, a halogen atom, C_{1-6} alkoxy, hydroxy or C_{1-6} alkyl;
 R^3 represents the group



R^4 and R^5 , which may be the same or different, each independently represents a hydrogen atom, a halogen atom, hydroxy, C_{1-6} alkoxy or C_{1-6} alkyl;
 Het represents a group selected from



- 20 R^6 represents a hydrogen atom, $-NR^9R^{10}$ or C_{1-6} alkyl optionally substituted by one or two substituents selected from C_{1-6} alkoxy, hydroxy and $-OCOR^{11}$;

R^{6a} and R^{6b}, which may be the same or different, each independently represent a hydrogen atom, a hydroxy group or C₁₋₆alkyl optionally substituted by one or two substituents selected from C₁₋₆alkoxy and hydroxy;

R⁷, R⁸ and R⁹, which may be the same or different, each independently represent a hydrogen atom or a C₁₋₆alkyl group;

R¹⁰ represents a hydrogen atom C₁₋₆alkyl, COR¹¹, benzoyl or -SO₂R¹¹;

R¹¹ represents C₁₋₆alkyl or phenyl;

V and W, which may be the same or different, each independently represent an oxygen or a sulphur atom;

X represents an oxygen atom or the group NR⁸ or S(O)_k;

Y represents an oxygen atom or the group NR⁸ or SO₂;

Z represents a sulphur atom or the group NR⁸;

k represents zero, 1 or 2; and

the dotted line represents a double bond present in either of the positions indicated.

It is to be understood that the present invention encompasses all geometric and optical isomers of the compounds of general formula (I) and their mixtures including the racemic mixtures thereof.

Salts of the compounds of formula (I) will preferably be pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g. magnesium), ammonium and NR₄⁺ (where R is C₁₋₄alkyl) salts.

In the compounds of general formula (I), the term 'C₁₋₆alkyl' or 'C₁₋₆alkoxy' as a group or part of a group means that the group is straight or branched and consists of 1 to 6 carbon atoms. Examples of suitable alkyl groups include methyl, ethyl, n-

propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy. The term 'halogen' means fluorine, chlorine, bromine or iodine.

- 5 It will be appreciated that R^6 , R^{6a} and R^{6b} may be attached to any available carbon atom in the group Het. R^{6a} and R^{6b} may be attached either to the same or different carbon atoms.

10 It will be further appreciated that where R^{6a} or R^{6b} is hydroxy, this may exist in the form of an oxo group where such keto tautomers are stable.

A preferred group of compounds of general formula (I) is that wherein the group Het, as defined above, on the phenyl ring B is attached at a position meta or para to the phenyl ring A in general formula (I).

- 15 A preferred group of compounds of general formula (I) is that wherein the group Het on the phenyl ring B is attached at the position para to the phenyl ring A in general formula (I).

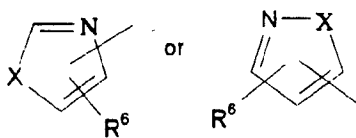
20 A further preferred group of compounds of general formula (I) is that wherein the group Het on the phenyl ring B is attached at the position para to the phenyl ring A in general formula (I).

25 Another preferred group of compounds of general formula (I) is that wherein one of R^{2a} and R^{2b} on the phenyl ring B is attached at a position ortho to the phenyl ring A in general formula (I). Preferably one of R^{2a} and R^{2b} represents H and the other of R^{2a} and R^{2b} represents H or C_{1-6} alkyl, such as methyl.

Also preferred are those compounds of general formula (I) wherein R^1 represents a hydrogen atom or C_{1-6} alkyl, especially methyl.

30 Another preferred group of compounds of general formula (I) is that wherein R^1 is attached at a position ortho to the phenyl ring B in general formula (I).

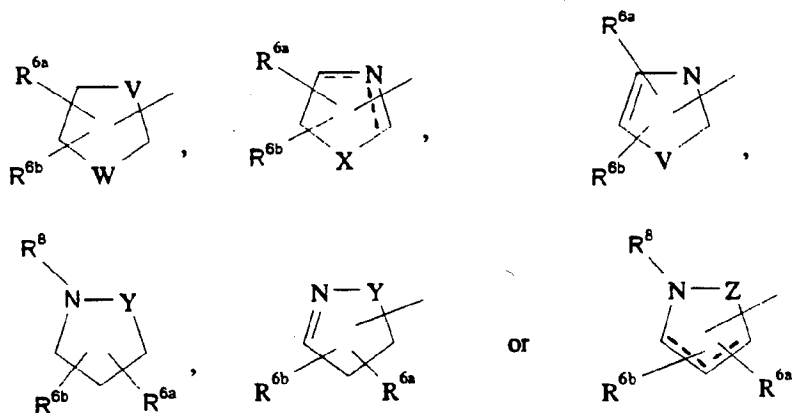
35 One sub group of compounds according to the invention is represented by compounds of formula (I) wherein Het represents a group



wherein X and R⁶ are as previously defined.

Preferably R⁶ represents a hydrogen atom or C₁₋₆alkyl, especially methyl, optionally substituted by C₁₋₆alkoxy, especially methoxy. More preferably R⁶ is a hydrogen atom or a methyl group.

A further sub group of compounds according to the invention is represented by compounds of formula (I) where Het represents a group



Preferably R^{6a} and R^{6b} each independently represent a hydrogen atom or C₁₋₆alkyl, especially methyl, optionally substituted by C₁₋₆alkoxy, especially methoxy. More preferably R^{6a} and R^{6b} each independently represent a hydrogen atom or a methyl group.

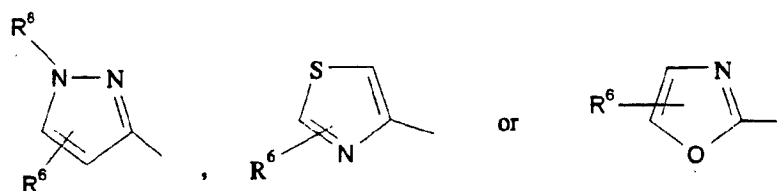
Preferably R⁴ is attached at the para-position relative to the amide linkage.

Another preferred group of compounds of general formula (I) is that wherein R⁴ is a halogen atom, especially a fluorine or chlorine atom, or a hydroxy or C₁₋₆alkoxy, especially methoxy, group. More preferably R⁴ represents methoxy.

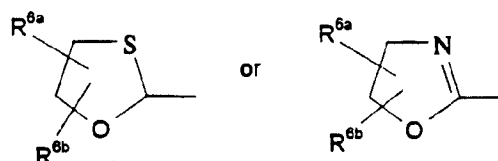
Preferably R⁵ is a hydrogen atom.

Another preferred group of compounds of general formula (I) is that wherein Het

represents the group



- 5 A yet further preferred group of compounds of general formula (I) is that wherein Het represents a group



- 10 Preferably R^7 is C_{1-3} alkyl, especially methyl.

Preferably R^8 represents a hydrogen atom or C_{1-3} alkyl, especially methyl.

Particularly preferred compounds of general formula (I) include:-

15

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2-methyl-4'-(1-methyl-1H-pyrazol-3-yl)[1,1'-biphenyl]-4-carboxamide;

20

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(2-methyl-4-thiazolyl)[1,1'-biphenyl]-4-carboxamide;

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(2-oxazolyl)[1,1'-biphenyl]-4-carboxamide;

25

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-2-oxazolyl)[1,1'-biphenyl]-4-carboxamide;

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(1,3-oxathiolan-2-yl)[1,1'-biphenyl]-4-carboxamide;

30

4'-(4,5-dihydro-2-oxazolyl)-N-[4-methoxy-3-(4-methyl-1-piperaziny)phenyl]-2'-methyl[1,1'-biphenyl]-4-carboxamide;

and their physiologically acceptable salts and solvates.

5

5-Hydroxytryptamine (serotonin) is a neurotransmitter which is widely distributed within the central nervous system (CNS), platelets and the gastrointestinal tract. Changes in transmission in serotonergic pathways in the CNS are known to modify, for example, mood, psychomotor activity, appetite, memory and blood
10 pressure. Release of 5-hydroxytryptamine from platelets can mediate vasospasm while changes in free 5-hydroxytryptamine levels in the gastrointestinal tract can modify secretion and motility.

Abundant pharmacological studies have led to the discovery of multiple types of
15 receptors for 5-hydroxytryptamine, thus providing a molecular basis to the diversity of its actions. These receptors are classed as 5-HT₁, 5-HT₂ and 5-HT₃, with 5-HT₁ receptors being sub-classified as 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D} and 5-HT_{1D}(like) receptors. The identification of these classes and sub-classes of receptor is based mainly on radiological binding studies.

20

Compounds having a selective antagonist action at 5-HT_{1D} receptors such as those described herein may exhibit a beneficial effect on subjects suffering from CNS disorders.

25 In the present specification, a 5-HT_{1D} antagonist is a non-naturally occurring (synthetic) compound that specifically and selectively antagonises 5-HT_{1D} receptors, i.e. - blocks the specific actions of 5-hydroxytryptamine mediated by the 5-HT_{1D} receptor. Such compounds may be identified by a high level of affinity ($pK_i \geq 8$) in the in vitro human cortex and guinea-pig striatum radioligand binding
30 assays described by Hoyer et al, Neuroscience Letters, 1988, 85, p357-362. Activity at 5-HT_{1D} receptors may be confirmed in vivo using the guinea pig rotation model described by G A Higgins et al, Br. J. Pharmacol., 1991, 102, p305-310.

35 Thus, for example, the following data have been generated in vitro using the guinea pig striatum radioligand binding assay described by Hoyer et al (supra) for

the compounds of the Examples:

<u>Example Number</u>	<u>PKi</u>
1	7.8
2	7.5
3	8.5
4	7.2
5	8.2
6	7.7
7	7.9
8	8.6
9	8.3
10	7.5

- 5 The affinity of a compound for 5-HT_{1A}, 5-HT_{1C} and/or 5-HT₂ receptors is measured using the in vitro tests described in the following publications:

	5-HT _{1A}	Gozlan <u>et al</u> , <u>Nature</u> , 1983, <u>305</u> , p140-142
	5-HT _{1C}	Pazos <u>et al</u> , Eur. J.Pharmacol., 1984, <u>106</u> , p531-538
10	5-HT ₂	Humphrey <u>et al</u> , Br. J. Pharmacol, 1988, <u>94</u> , p1123-1132 (rabbit aorta model).

15 Thus, for example, compounds of the present invention have been shown to inhibit 5-hydroxytryptamine induced contraction of the dog isolated saphenous vein and to antagonise the 5-hydroxytryptamine induced inhibition of neurotransmission in central and peripheral neurones.

20 5-HT_{1D} antagonists, and in particular the compounds of the present invention, may therefore be of use in the treatment of CNS disorders such as mood disorders, including depression, seasonal affective disorder and dysthymia; anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnesic disorders and age-associated memory impairment; and disorders of eating behaviour, including anorexia

nervosa and bulimia nervosa. Other CNS disorders include Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

5 5-HT_{1D} antagonists, and in particular compounds of the present invention, may also be of use in the treatment of endocrine disorders such as hyperprolactinaemia, the treatment of vasospasm (particularly in the cerebral vasculature) and hypertension, as well as disorders in the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in
10 the treatment of sexual dysfunction.

Therefore, according to a second aspect of the invention, we provide a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy.

15 According to a further aspect of the present invention, we provide a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

20 According to another aspect of the invention, we provide the use of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a therapeutic agent for the treatment of the aforementioned disorders.

25 According to a further aspect of the invention, we provide, a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such treatment of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof.

30 In particular, according to another aspect of the invention, we provide a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of depression.

35 It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established symptoms.

It will be appreciated that the compounds according to the invention may

advantageously be used in conjunction with one or more other therapeutic agents,

for instance, different antidepressant agents such as tricyclic antidepressants (e.g. amitriptyline, dothiepin, doxepin, trimipramine, butriptyline, clomipramine, 5 desipramine, imipramine, iprindole, lofepramine, nortriptyline or protriptyline), monoamine oxidase inhibitors (e.g. isocarboxazid, phenelzine or tranylcyclopramine) or 5-HT reuptake inhibitors (e.g. fluvoxamine, sertraline, fluoxetine or paroxetine), and/or antiparkinsonian agents such as dopaminergic antiparkinsonian agents (e.g. levodopa, preferably in combination with a 10 peripheral decarboxylase inhibitor e.g. benserazide or carbidopa, or a dopamine agonist e.g. bromocriptine, lysuride or pergolide). It is to be understood that the present invention covers the use of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof in combination with one or more other therapeutic agents.

15 Thus there is provided in a further or alternative aspect of the present invention a compound of general formula (I) or a physiologically acceptable salt or solvate thereof and an antidepressant agent in the presence of each other in the human or non-human animal body for use in the treatment of the aforementioned disorders.

20 In a particular aspect of the present invention there is provided a compound of general formula (I) or a physiologically acceptable salt or solvate thereof and an antiparkinsonian agent such as a dopaminergic antiparkinsonian agent, e.g. levodopa, and a peripheral decarboxylase inhibitor, e.g. benserazide or carbidopa, 25 or a dopamine agonist e.g. bromocriptine, lysuride or pergolide in the presence of each other in the human or non-human animal body for use in the treatment of Parkinson's disease, dementia in parkinsonism, neuroleptic induced parkinsonism and tardive dyskinesias.

30 In using a compound of general formula (I) or a physiologically acceptable salt or solvate thereof and one or more therapeutic agents it may be preferable to employ the active ingredients in the form of separate pharmaceutical formulations. A combined formulation can be used, however, in such a combined formulation the active ingredients must of course be stable and mutually compatible in the 35 particular formulation employed.

It will be appreciated that administration of the active ingredients to a human or non-human patient may be simultaneous, separate or sequential. Where administration is not simultaneous, the delay in administering the second of the active ingredients should not be such as to lose the beneficial effect of the combination.

While it is possible that a compound of general formula (I) may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The compounds of general formula (I) and their physiologically acceptable salts and solvates may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions comprising at least one compound of general formula (I) or a physiologically acceptable salt or solvate thereof. Such compositions may be presented for use in a conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Thus, the compositions according to the invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation. Oral administration is preferred.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, orbital, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives

such as suspending agents, for example, sorbitol syrup, methylcellulose, glucose/sugar syrup, gelatin, hydroxypropyl methylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-
5 aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

10 For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition according to the invention may be formulated for parenteral
15 administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the
20 active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For administration by inhalation either orally or nasally the compositions according to the invention are conveniently delivered in the form of an aerosol spray
25 presentation from pressurised packs with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

30 Alternatively, for administration by inhalation the compositions according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example,
35 capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

The pharmaceutical formulations according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

5 The compositions according to the invention may be prepared by mixing the various ingredients using conventional means.

It will be appreciated that the amount of a compound of general formula (I) required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being
10 treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or veterinarian. In general, however, a proposed dose of the compounds of the invention for administration in man is 0.5 to 1000mg, preferably 1 to 200mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

15

The compounds of the invention may be prepared by a number of processes as described in the following. In describing the processes which may be used for preparing the compounds of general formula (I) or intermediates useful in the preparation thereof, any of R¹-R¹¹, Het, V, W, X, Y Z, and k in the various
20 formulae are as defined in general formula (I) unless otherwise stated.

It will be appreciated that in the following methods for the preparation of compounds of general formula (I), for certain reaction steps it may be necessary to protect various reactive substituents in the starting materials for a particular
25 reaction and subsequently to remove the protecting group. Such protection and subsequent deprotection may be particularly pertinent where R⁷, R⁸, R⁹ and/or R¹⁰ in intermediates used to prepare compounds of general formula (I) are hydrogen atoms. Standard protection and deprotection procedures can be employed, for example formation of a phthalimide (in the case of a primary amine),
30 benzyl, trityl, benzyloxycarbonyl or trichloroethoxycarbonyl derivatives. Subsequent removal of the protecting group is achieved by conventional procedures. Thus a phthalimide group may be removed by treatment with hydrazine or a primary amine, for example methylamine. Benzyl or benzyloxycarbonyl groups may be removed by hydrogenolysis in the presence of
35 a catalyst e.g. palladium, and trichloroethoxycarbonyl derivatives may be removed by treatment with zinc dust. Trityl groups may be removed under acidic conditions

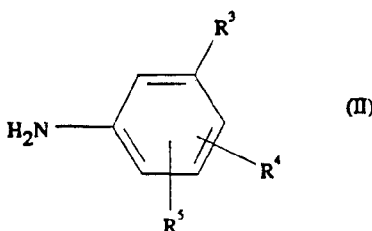
using standard procedures.

It may also be necessary in some cases to protect carboxylic acid groups (e.g. as esters) or aldehyde or ketone groups (e.g. as acyclic or cyclic acetals or ketals or as thioacetals or thioketals). Subsequent removal of these protecting groups is achieved by conventional procedures. Thus for example alkyl esters may be removed under conditions of acidic or basic hydrolysis, benzyl esters may be removed by hydrogenolysis in the presence of a catalyst e.g. palladium. Acyclic or cyclic acetals or ketals may be removed under conditions of acidic hydrolysis and thioacetals and thioketals may be removed using a mercuric salt.

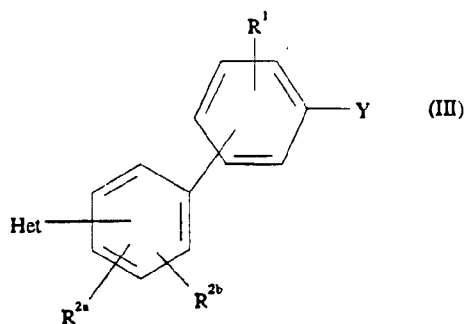
Hydroxyl groups may also need protection and these may be adequately protected under amenable conditions as their esters or trialkylsilyl, tetrahydropyran and benzyl ethers. Such derivatives may be deprotected by standard procedures.

Conventional protecting groups are described, for example, in "Protective Groups in Organic Chemistry" Ed. J F W McOmie (Plenum Press 1973) and "Protective Groups in Organic Synthesis" by T. W. Green and P.G.M. Wuts (John Wiley & Sons, 1991)

According to one general process (1), the compounds of general formula (I) may be prepared by a carbonylation reaction involving an aniline (II)



and a halophenyl compound (III)

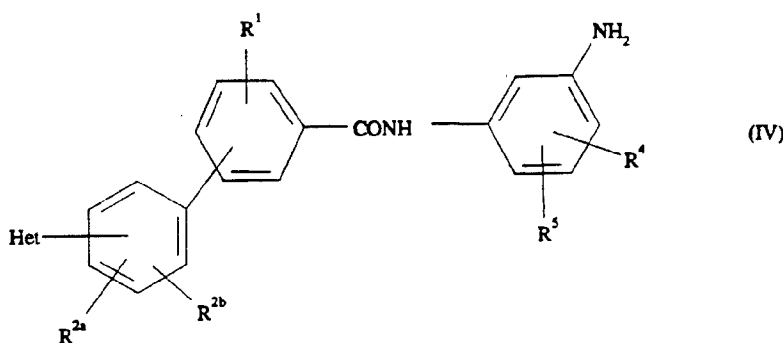


(where Y represents a halogen atom e.g. bromine or iodine or the group -OSO₂CF₃).

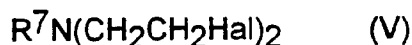
The reaction takes place, for example, in the presence of carbon monoxide using a palladium salt as a catalyst. The reaction is effected in the presence of a suitable base e.g. a tertiary amine such as triethylamine or tri-n-butylamine and may be conducted in a suitable solvent such as an amide e.g. dimethylformamide or a nitrile eg acetonitrile at a temperature within the range of -10°C to +120°C.

Suitable palladium salts for the reaction include triarylphosphine palladium (II) salts such as bis(triphenylphosphine)palladium (II) chloride.

According to another general process (2), the compounds of general formula (I) may be prepared by treating a compound of formula (IV)



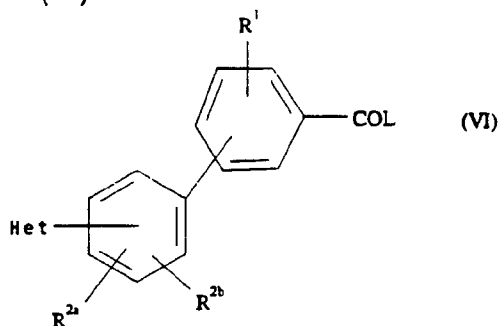
with an amine dihalide of formula (V)



(where Hal is a chlorine, bromine or iodine atom).

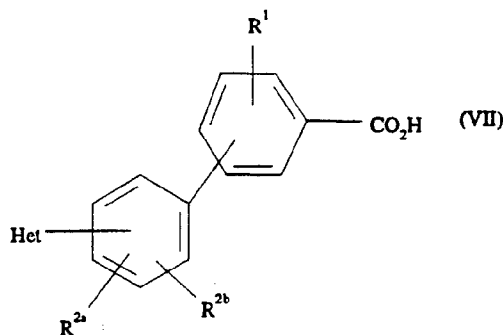
The reaction is conveniently effected in a polar solvent such as an alcohol (e.g. n-butanol) or a nitrile (e.g. acetonitrile), optionally in the presence of a base, for example, an alkali metal carbonate such as sodium carbonate or potassium carbonate, or alternatively in a non-polar solvent (e.g. chlorobenzene) in the absence of a base. The reactions may conveniently be carried out at an elevated temperature, for example, the reflux temperature of the chosen solvent.

According to another general process (3), the compounds of general formula (I) may be prepared by reacting an aniline of formula (II) with an activated carboxylic acid derivative of formula (VI)



(where L is a leaving group).

Suitable activated carboxylic acid derivatives represented in formula (VI) include acyl halides (e.g. acid chlorides) and acid anhydrides including mixed anhydrides. These activated derivatives may be formed from the corresponding acid of formula (VII)



by well known procedures. For example, acid chlorides may be prepared by reaction with phosphorus pentachloride, thionyl chloride or oxalyl chloride and

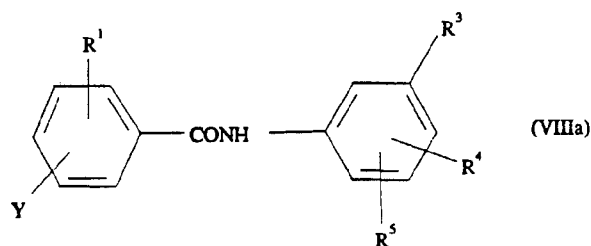
acid anhydrides may be prepared by reaction with an appropriate acid anhydride (e.g. trifluoroacetic anhydride), an acid chloride (e.g. acetyl chloride), an alkyl or aralkyl haloformate (e.g. ethyl or benzyl chloroformate) or methanesulphonyl chloride.

Activated carboxylic acid derivatives of formula (VI) may also be prepared in situ by the reaction of the corresponding acids of formula (VII), with a coupling reagent such as carbonyldiimidazole, dicyclohexylcarbodiimide or diphenylphosphorylazide.

The conditions under which the activated carboxylic acid derivatives of formula (VI) are formed and subsequently reacted with the anilines of formula (II) will depend upon the nature of the activated derivative. However, in general the reaction between the compounds (II) and (VI) may be carried out in a non-aqueous medium such as, for example, dimethylformamide, tetrahydrofuran, acetonitrile or a halohydrocarbon such as dichloromethane at a temperature within the range -25°C to $+150^{\circ}\text{C}$. The reaction may optionally be carried out in the presence of a base such as triethylamine or pyridine and the base may also be used as the solvent for reaction.

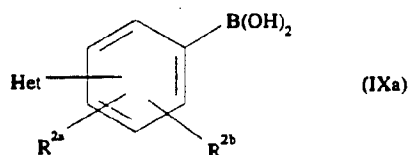
Where acid chlorides are used, the reaction may be carried out using the Schotten-Baumann technique in the presence of a suitable base, for example, aqueous sodium hydroxide, conveniently at a temperature between 0°C and 100°C , for example, room temperature.

According to another general process (4a), the compounds of general formula (I) may be prepared by treating a compound of formula (VIIIa)



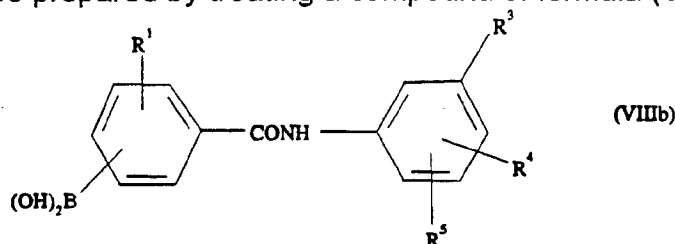
(where Y represents a bromine or iodine atom or the group $-\text{OSO}_2\text{CF}_3$) with a

compound of formula (IXa)



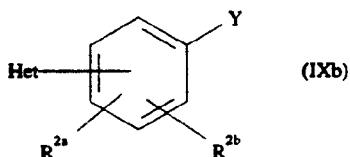
5 or an ester, an anhydride or a salt (e.g. lithium) thereof.

Alternatively, according to the general process (4b), the compounds of general formula (I) may be prepared by treating a compound of formula (VIIIb)



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or an ester, an anhydride or a salt (e.g. lithium) thereof, with a compound of formula (IXb)



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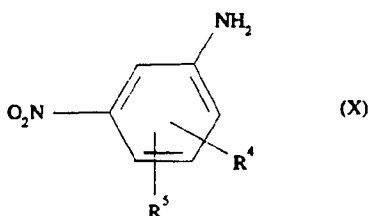
where Y represents a bromine or iodine atom or the group -OSO₂CF₃.

Both reactions may be effected in the presence of a transition metal catalyst such as (Ph₃P)₄Pd (where Ph represents phenyl) in a suitable solvent such as an ether (eg 1,2-dimethoxyethane or tetrahydrofuran) in the presence or absence of water, or an aromatic hydrocarbon (eg benzene). The reaction is preferably carried out in the presence of a base such as an alkali or alkaline earth metal carbonate (eg sodium carbonate) at a suitable temperature up to reflux.

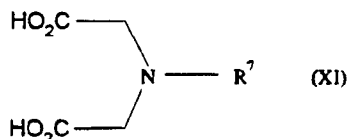
25 Compounds of general formula (I) may also be prepared from other compounds of formula (I) by standard methods of interconversion. For instance, when R^{2a} or R^{2b} represents a hydroxy or alkoxy group and/or when R⁴ and/or R⁵ represents

hydroxy or alkoxy these groups may be interchanged by standard methods of O-alkylation or O-dealkylation. Thus, for example, a compound in which R^4 represents hydroxy may be prepared by treating a corresponding compound in which R^4 represents methoxy with a reagent system capable of removing the methyl group e.g. a mercaptide such as sodium ethylmercaptide in a solvent such as dimethylformamide, lithium iodide in collidine, boron tribromide in a halohydrocarbon solvent e.g. methylene chloride or molten pyridine hydrochloride.

Intermediates of formula (II) may be prepared from the corresponding compound of formula (X)



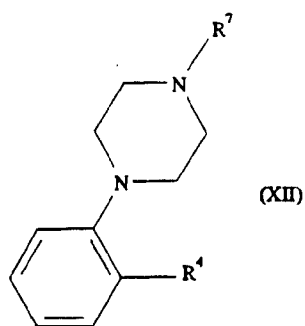
by reaction with a compound of formula (XI)



in the presence of acetic anhydride, followed by reduction of the diketopiperazine intermediate thus formed using, for example, borane. The reaction may be carried out at a temperature between 50°C and reflux, and optionally in a solvent such as an ether, e.g. tetrahydrofuran, or toluene. The nitro group may be subsequently converted into an amine using standard methodology.

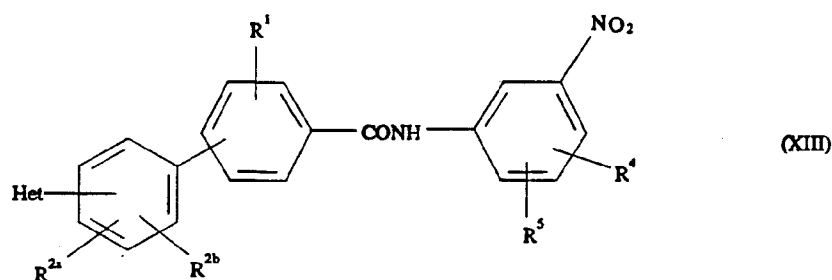
Alternatively, intermediates of formula (II) in which R^4 is adjacent to R^3 , and R^5 is a hydrogen atom, may be prepared by nitration of a compound of formula (XII)

21



using an appropriate nitrating system such as sulphuric acid and potassium nitrate, or nitronium tetrafluoroborate, in the presence of a solvent, for example, acetonitrile followed by reduction of the nitro group using standard methodology.

Intermediates of formula (IV) may be prepared by reduction of the corresponding nitro compound of general formula (XIII)



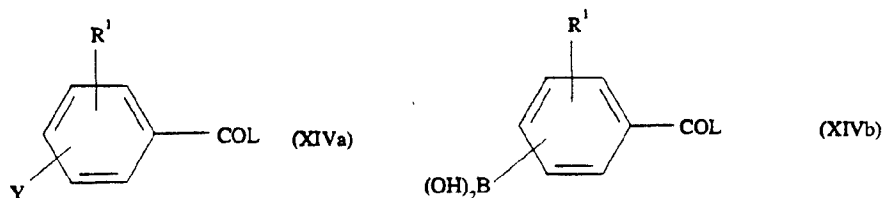
The reduction may be effected by catalytic hydrogenation using a metal catalyst such as palladium or platinum or oxides thereof, preferably, in a solvent such as an alcohol e.g ethanol, or alternatively by using Raney nickel and hydrazine in a solvent such as an alcohol e.g. ethanol, or alternatively by using titanium trichloride in a suitable solvent such as aqueous acetone.

Intermediates of formula (XIII) may be prepared by condensing a compound of formula (VI) with a compound of formula (X) under the conditions of general process (3).

It will be appreciated that, where necessary, a halogen substituent may be converted into a carboxyl group using standard methodology thus, for example, intermediates of formula (VII) may be prepared from an intermediate of formula (III) by lithiation using, for example, n-butyl lithium followed by quenching with

carbon dioxide.

Intermediates of formula (VIIIa) and (VIIIb) may be prepared by reaction of a compound of formula (II) with a compound of formula (XIVa) or (XIVb), respectively,



according to the method of general process (3).

- 10 The boronic acid intermediates of formulae (VIIIb), (IXa) and (XIVb) or their esters, anhydrides or salts may be used in situ under the conditions described above for general process (4).

15 Intermediates of formula (VII) may be prepared by the reaction of a compound of formula (IXa) or (IXb) with a compound corresponding formula (XIVa) or (XIVb) in which L represents a hydroxy group, respectively, according to the method of general process (4).

20 Intermediates of formula (II) may also be prepared from the corresponding carboxylic acid using conventional procedures (e.g. by Curtius rearrangement).

Intermediates of formulae (V), (X), (XI), (XII), (XIVa) and (XIVb) are either known compounds or may be prepared by standard methodology or methods analogous to those described herein.

25

Intermediates containing the group Het may be prepared by methods described herein and using techniques well known in the art, such as those described in "Comprehensive Organic Chemistry", Vol. 4 by D. Barton and W.D. Ollis, Pergamon Press, Oxford (1979) (see especially pages 1020-1050 for five-membered mixed heteroatom ring systems) or in "Comprehensive Heterocyclic Chemistry", Vol. 6 by A R Katritzky and C W Rees, Pergamon Press, Oxford (1984) (see pages 365-577).

30

Acid addition salts of the compounds of general formula (I) may be prepared by treating the corresponding free base with a suitable acid using conventional methods. Thus, for example, a generally convenient method of forming the acid addition salts is to mix appropriate quantities of the free base and the acid in an appropriate solvent eg an alcohol such as ethanol or an ester such as ethyl acetate.

Salts of compounds of general formula (I) may also be converted to different salts of compounds of general formula (I) using conventional methods.

The invention is illustrated but not limited by the following examples in which temperatures are in °C. Thin layer chromatography (T.l.c.) was carried out on silica plates.

The following abbreviations are used :-

DMF - dimethylformamide; TEA - triethylamine; HMPA - hexamethylphosphoramide; THF - tetrahydrofuran; MSC - methanesulphonyl chloride; BTPC - bis(triphenylphosphine)palladium (II) chloride; DMA - dimethylamine; SPC - Short path chromatography carried out on silica (Merck 7747) unless otherwise stated. FCC - Flash column chromatography carried out on silica (Merck 9385). 'Dried' refers to drying using sodium sulphate or magnesium sulphate unless otherwise stated.

The following solvent systems were used:-

System A - dichloromethane:ethanol:0.88 ammonia; System B - dichloromethane:methanol:0.88 ammonia.

Intermediate 1

Methyl 4-methoxy-3-(4-methyl-1-piperazinyl)benzoate hydrochloride

A suspension of 2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride (1.92g) and methyl 3-amino-4-methoxybenzoate (1.81g) in n-butanol was refluxed with stirring for 19h. Anhydrous sodium carbonate (0.54g) was added and refluxing continued for 8.5h. The solvent was then removed to give an oil which was taken up in water (50ml) and 2N hydrochloric acid (50ml) and extracted with ethyl acetate (2x50ml). The acid solution was then basified with sodium

bicarbonate and re-extracted with ethyl acetate (3x50ml). The extracts were dried and concentrated to a semi-solid (2.47g) which was absorbed from System A (200:8:1) (5ml) onto Kieselgel G (100g). Elution with the same solvent gave starting material and minor basic impurities. Further elution with System A (100:8:1) (450ml) gave first minor impurities and later fractions afforded the free base of the desired product as a gum (0.48g). This was taken up in methanol (5ml), filtered and treated with ethereal hydrogen chloride and diluted to 25ml with ethyl acetate. A cream coloured solid separated, was filtered and the solid (0.586g) recrystallised from methanol:ethyl acetate to give the title compound m.p. 202-204°C.

Intermediate 2

4-Methoxy-3-(4-methyl-1-piperazinyl)benzoic acid hydrazide

The free base of Intermediate 1 (2g) in methanol (20ml) was treated with hydrazine hydrate (4ml) and refluxed under nitrogen for 16h. The solution was evaporated and then adsorbed from ethanol onto silica gel [Merck Art. 7734, 5g]. Purification by SPC eluting with System A (91:9:0.9) gave the title compound as an off-white solid (0.764g).

T.l.c. System A (90:10:0.1), Rf 0.2.

Intermediate 3

4-Methoxy-3-(4-methyl-1-piperazinyl)benzenamine

A solution of Intermediate 2 (0.73g) in water (30ml) was mixed with concentrated hydrochloric acid (0.6ml), the solution cooled to 0 to 5°C and a solution of sodium nitrite (0.219g) in water (10ml) added during 5min. The solution was stirred at 0-5°C for 20min, then 1h at 23°C, and treated with concentrated hydrochloric acid (40ml) and acetic acid (40ml). The mixture was heated at reflux for 2h, cooled and poured into aqueous sodium hydroxide (5N; 260ml). The mixture was extracted with ethyl acetate (3x500ml), and the combined, dried organic extracts were evaporated to give the title compound as a gum (0.190g).

T.l.c. System A (95:5:0.5), Rf 0.2.

Intermediate 3 was also made by the alternative two-step reaction as follows:-

(a) 1-Methyl-4-(2-methoxy-5-nitrophenyl)piperazine

1-(2-Methoxyphenyl)-4-methylpiperazine (5.36g) was acidified with 5N sulphuric

acid and the excess water evaporated in vacuo. Concentrated sulphuric acid (95-98%, 22ml) was added and the mixture stirred at room temperature until homogeneous. To the stirred, dark solution was added portionwise at room temperature potassium nitrate (3.07g) in ten portions at intervals of approximately 5min. The mixture was stirred at room temperature for 4h then poured onto ice (~500ml) and the mixture made slightly alkaline with anhydrous sodium carbonate. The basic mixture was extracted with ethyl acetate (4x150ml) and the combined extracts dried. After 1h the mixture was filtered and the filtrate evaporated to dryness in vacuo. The dark red residue was diluted with ether (200ml) and the solid which separated (0.51g) was filtered off and discarded. The filtrate was evaporated to dryness and the oily residue mixed with ether (300ml) and the suspension filtered. The filtrate was evaporated to dryness to give a red gum which very slowly solidified to give the title compound (5.45g)

T.l.c. System A (150:8:1), Rf 0.45

(b) 4-Methoxy-3-(4-methyl-1-piperazinyl)benzeneamine

To a solution of the product of step (a) (5.07g) in ethanol (70ml) was added a paste of Raney Nickel in water (2g). To the warmed suspension was added, with constant agitation, hydrazine hydrate (5ml) dropwise during 20min with occasional warming. After the main effervescence had ceased, the suspension was heated for 15min and then filtered with the aid of ethanol under nitrogen. The residues were kept moist and washed with ethanol and the combined filtrate and washings were evaporated to dryness with the aid of ethanol. The dark residue was re-evaporated with ethanol (20ml), resuspended in ether (40ml) and the mixture filtered. The residue was washed with ether and dried to give a solid consisting of the title compound (2.365g)

T.l.c. System A (70:8:1), Rf 0.25.

Intermediate 4

4-Bromo-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]benzamide

A solution of Intermediate 3 (0.168g) in pyridine (3ml) was treated with 4-bromobenzoyl chloride (0.25g) and stirred at 110⁰, under nitrogen, for 5h. Sodium bicarbonate (20ml; 8%) was added and the mixture was evaporated. The residue was pre-adsorbed onto silica gel [Merck Art. 7734 ca. 5g] and purified by SPC eluting with System A (97:3:0.3) to give the title compound as a beige solid (0.237g), m.p. 158.5-159.5⁰C.

Intermediate 5

[4-[[[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]amino]carbonyl] phenyl]boronic acid

5 n-Butyllithium (7.5ml of 1.6M solution in hexane) was added dropwise at -90 to -100° to a stirred solution of Intermediate 4 (404mg) and triisopropylborate (2.77ml) in dry THF (20ml) over 45min under nitrogen, and stirring continued for 1.5h at -90 to -103° for 1.5h. After 3h at -78°, the cooling bath was removed and the mixture stirred at +23° for 11h. Water (4ml) was added, and, after 1h, the
10 mixture was evaporated. The residue was adsorbed from System A (50:45:5) onto silica gel (Merck 7734, 10ml) and purified by FCC eluting with System A (89:10:1 _ 50:45:5) to give firstly recovered impure starting material followed by the title compound as a cream foam (280mg)

T.1.c. System A (50:45:5) Rf 0.04

Intermediate 6

4-Bromo-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-3-methylbenzamide

4-Bromo-3-methylbenzoic acid (4.86g) in an excess of thionyl chloride (25ml) was heated at reflux for 1h. The excess thionyl chloride was then removed by
20 distillation and evaporation. The resultant acid chloride was added to a mixture of a solution of Intermediate 3 (5.0g) in THF (25ml) and sodium hydroxide (1.8g) in water (30ml). After stirring, under nitrogen, overnight at room temperature the solvent was removed by evaporation, water (40ml) added and the mixture extracted with dichloromethane (5x50ml), dried and evaporated to give a
25 brown/orange sticky foam. This was purified by FCC eluting with system B (970:20:10) to give the title compound (5.73g).

T.1.c. System B (970:20:10) Rf=0.11.

Intermediate 7

30 [4-[[[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]amino]carbonyl]-2-methylphenyl]boronic acid

Intermediate 6 (5.77g) was treated according to the method of Intermediate 5 to give title compound (1.87g) as a pale yellow foam. T.1.c. System B (890:100:10) Rf = 0.07

Intermediate 8

4-(4-Bromophenyl)-1-methyl-1H-imidazole

Sodium hydride (429mg of a 60% dispersion in oil) was washed under nitrogen with hexane (3x4ml) and then treated dropwise with a solution of 4-(4-bromophenyl)-1H-imidazole (2.00g) in dry DMF (20ml) with stirring at 20 to 25^o (ice cooling). After 30 min at 23^o, iodomethane (0.61ml) was added dropwise over 5min at 5 to 12^o, and the mixture stirred at 23^o for 16h. Water (2ml) was added and the mixture evaporated. The residue was treated with water (20ml), extracted with ethyl acetate (2x60ml), and the combined, dried organic extracts were evaporated. The residue was crystallised from ethyl acetate (5ml) to give the title compound as fine white needles (770mg) m.p. 136-137.5^o.

Intermediate 94-Bromo-3-methyl-N-(2-oxopropyl)benzamide

To a solution of 4-bromo-3-methylbenzoic acid (2.5g) in dry acetonitrile (20ml) was added triethylamine (2.43ml) followed dropwise by isobutylchloroformate (2.26ml). The mixture was stirred for 30min and then 2-hydroxypropanamine (1.79ml) was added dropwise. The mixture was left to stand overnight, filtered, and water (75ml) added to the residue which was then extracted with ethyl acetate (2x75ml). The dried extracts were evaporated to give an off-white solid (2.18g). Dry DMSO (0.95ml) was added dropwise to a cold (-60^o) stirred solution of oxalyl chloride (1.03ml) in dry dichloromethane (20ml). The mixture was stirred for 15min and a solution of the above solid (1.48g) in dry dichloromethane (20ml) was added. The mixture was stirred at -60^o for 3h and then triethylamine (7.4ml) was added and the temperature allowed to rise to 20^o. Water (50ml) was added, the mixture extracted with dichloromethane (2x50ml) and the extracts dried and evaporated to give a yellow solid (2.2g). This material was purified by FCC eluting with ethyl acetate:hexane (2:1) to give the title compound as a pale yellow solid (743mg) m.p. 129-131^o.

Intermediate 102-(4-Bromo-3-methylphenyl)-5-methyloxazole

Intermediate 9 (726mg) was stirred in conc. sulphuric acid (6ml) for 45min. The mixture was poured into water (120ml) and then extracted with ethyl acetate (2x70ml). The dried extracts were evaporated to give an off-white solid (650mg). This material was chromatographed on silica gel eluting with ethyl acetate:hexane (1:2) to give the title compound as a pale yellow crystalline solid (533mg) m.p. 37-

38°.

Intermediate 11

5-(4-Bromophenyl)-2,4-dimethyloxazole

5 A solution of 1-(4-bromophenyl)-1-propanone (636mg) in dry acetonitrile (40ml) containing trifluoroacetic acid copper (2+) salt (2.16g) and 4-methylbenzene sulphonic acid (catalytic amount) was heated at reflux under nitrogen for 4h. The cooled mixture was partitioned between 2N sodium carbonate (50ml) and ether (2x40ml). The dried extracts were evaporated to give a brown solid which was
10 chromatographed on silica gel eluting with ethyl acetate:hexane (1:4) to give the title compound as red/brown solid (261mg).
T.l.c. ethyl acetate:hexane (1:4) Rf 0.18.

Intermediate 12

2-Bromo-1-(4-bromo-3-methyl)ethanone

15 A mixture of 1-(4-bromo-3-methylphenyl)ethanone (0.962g) and copper (II) bromide (3.02g) in chloroform (10ml) and ethyl acetate (10ml) was heated at reflux under nitrogen with stirring for 20 hours. Two drops of a solution of hydrogen bromide (45%) in acetic acid were then added and the reaction heated at reflux for
20 a further 1.5 hours. A further quantity of copper (II) bromide (1.51g) was added and the mixture refluxed for a further 1.5 hours. The reaction was cooled and filtered and the filtrate evaporated in vacuo to give a two phase oil. This was chromatographed on silica (Merck 7729, 150g) eluting with hexane initially then with hexane:ethyl acetate (11:1). Evaporation of the eluate gave a pale yellow
25 solid (1.13g) containing the title compound contaminated with 2,2-dibromo-1-(4-bromo-3-methyl)ethanone.
T.l.c. hexane Rf 0.21 and Rf 0.20.

Intermediate 13

4-(4-Bromo-3-methylphenyl)-2-methylthiazole

30 A mixture of the unpurified product of Intermediate 12 (0.544g) and ethanethioamide (0.14g) in ethanol (6ml) was heated at reflux for 26.5 hours. The yellow solid which separated on cooling was filtered off and the filtrate evaporated in vacuo to give a yellow solid. This was purified by FCC eluting with
35 hexane:dichloromethane (1:1) to give the title compound (0.197g) as a yellow solid.

Found: C, 48.95; H, 3.8; N, 4.7
C₁₁H₁₀BrNS requires: C, 49.3; H, 3.8; N, 5.2%

Intermediate 14

4-Bromo-N-(2-hydroxyethyl)-3-methylbenzamide

To a solution of 4-bromo-3-methylbenzoic acid (2.5g) in dry acetonitrile (20ml) was added triethylamine (2.43ml) followed by the dropwise addition of ethyl chloroformate (1.66ml). The mixture was stirred for 30mins and then 2-aminoethanol (1.29ml) was added dropwise. The mixture was left at 20° for 18h and was then partitioned between water (100ml) and ethyl acetate (2x80ml). The dried ethyl acetate extracts were evaporated to give an off-white solid which was recrystallised from isopropyl acetate (25ml) to give the title compound as colourless crystals (1.98g), m.p. 119-121°C.

Intermediate 15

2-(4-Bromo-3-methylphenyl)-4,5-dihydrooxazole

Intermediate 14 (1.08g) was dissolved in thionyl chloride (5ml) and the mixture stirred at 20° for 1.5h. The mixture was added carefully to 2N sodium carbonate (100ml) and was then extracted with ethyl acetate (2x75ml). The dried extracts were evaporated to give a colourless solid. This material was chromatographed on silica gel (Merck 7729) eluting with ethyl acetate:hexane (1:2) to give the title compound as a colourless crystalline solid (487mg) m.p. 56-58°.

Intermediate 16

2-(4-Bromo-3-methylphenyl)oxazole

A solution of Intermediate 15 (150mg) in dry toluene (5ml) containing 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (156mg) was heated to reflux, under nitrogen, for 18h. The mixture was allowed to cool, and was partitioned between 2N sodium hydroxide (30ml) and ether (2x30ml). The dried ether extracts were evaporated to give an orange gum. This material was chromatographed on silica gel eluting with ethanol:hexane (1:4) to give the title compound as a red crystalline solid (48mg) T.l.c. ethyl acetate:hexane (1:4) R_f 0.43.

Intermediate 17

2-(4-Bromo-3-methylphenyl)-1,3-oxathiolane

A mixture of 4-bromo-3-methylbenzaldehyde (1g) and 2-mercaptoethanol (0.34ml)

in dichloromethane (20ml) under nitrogen, was cooled to 0°C and treated with boron trifluoride etherate (0.12ml). The mixture was stirred at 0°C for 1h, then at 20°C for 18h and was then washed with 2N sodium carbonate solution (40ml). The aqueous layer was extracted with dichloromethane (50ml) and the combined, dried extracts were evaporated to give a pale yellow oil (1.1g). Purification by FCC eluting with ethyl acetate:hexane (1:19) afforded the title compound as a colourless oil (635mg).

Analysis Found: C,46.05; H,4.2;
C₁₀H₁₁BrOS requires C,46.35; H,4.3%

Intermediate 18

(S)-4-Bromo-N-(2-hydroxypropyl)-3-methylbenzamide

To a solution of 4-bromo-3-methylbenzoic acid (500mg) in dry dichloromethane (10ml) and TEA (0.48ml) was added ethyl chloroformate (0.33ml). The mixture was stirred for 30mins and then (S)-1-amino-2-propanol (0.36ml) was added. The mixture was left for 1h and was then partitioned between water (40ml) and dichloromethane (2x40ml). The dried extracts were evaporated to give a pale yellow oil which crystallised on standing to give the title compound (650mg).

Assay Found: C,48.3; H,5.55; N,5.05;
C₁₁H₁₄BrNO₂ requires: C,48.55; H,5.2; N,5.15%

Intermediate 19

(S)-2-(4-Bromo-3-methylphenyl)-4,5-dihydro-5-methyloxazole

Intermediate 18 (300mg) was dissolved in thionyl chloride (2ml) and was stirred at 20°C for 2h. The mixture was then added carefully to 2N sodium carbonate solution (40ml) and was extracted with ethyl acetate (2x35ml). The dried extracts were evaporated to give a pale yellow oil. This material was purified by FCC eluting with ethyl acetate:hexane (3:1) to give the title compound as a colourless oil (181mg)

T.l.c. ethyl acetate:hexane (3:1) R_f 0.48

Example 1

N-[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2-methyl-4'-(1-methyl-1H-pyrazol-5-yl)[1,1'-biphenyl]-4-carboxamide

A mixture of sodium carbonate (141mg), 5-(4-bromophenyl)-1-methyl-1H-pyrazole (105mg), Intermediate 7 (190mg), tetrakis (triphenylphosphine)palladium (0)

(20mg), DME (10ml) and water (5ml) was stirred at reflux under nitrogen for 3h. The solution was evaporated, treated with water(20ml) and extracted with ethyl acetate (3x30ml). The combined, dried organic extracts were evaporated onto silica gel (Merck 7734, 3ml) and the resultant silica applied as a plug to a flash column of silica gel (Merck 9385). Gradient elution with System A (967:30:3→945:50:5) afforded a product (55mg) which on trituration with ether (4ml) afforded the title compound as fine white crystals (37mg), m.p. 207-209°C

Assay Found: C,72.6; H,6.9; N,13.6;

C₃₀H₃₃N₅O₂·0.11C₄H₁₀·0.05H₂O requires C,72.4;H,6.8; N,13.9%

Water Assay Found: H₂O, 0.24%w/w ≡ 0.05mol

Example 2

N-[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2-methyl-4'-(1-methyl-1H-imidazol-4-yl)[1,1'-biphenyl]-4-carboxamide

A solution of sodium carbonate (111mg) in water (5ml), followed by tetrakis(triphenylphosphine)palladium (0) (24mg) was added to Intermediate 8 (124mg), Intermediate 7 (200mg) and DME (10ml), and the stirred mixture heated at reflux under nitrogen for 22h. The cooled mixture was evaporated and the residue stirred in refluxing ethanol (80ml) for 5 min. Purification by FCC eluting with a gradient of System A (945:50:5_934:60:6) afforded a product. This was purified by SPC eluting with System A (956:40:4) and then further purified by thin layer chromatography eluting with chloroform:methanol:0.88 ammonia (912:80:8) to give the title compound as a cream-coloured solid (57mg).

T.l.c. System A (89:10:1) R_f 0.33.

n.m.r. (CDCl₃) δ 2.29 (3H,s), 2.41 (3H,s), 2.53 (4H,m), 3.04 (4H,m), 3.76 (3H,s), 3.82 (3H,s), 6.96 (1H,d), 7.44 (4H,m), 7.51 (1H,dd), 7.71 (2H,br.s), 7.89-7.95 (4H,m), 10.10 (1H,m).

Similarly prepared was:-

Example 3

N-[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2-methyl-4'-(1-methyl-1H-pyrazol-3-yl)[1,1'-biphenyl]-4-carboxamide as a cream-coloured foam (67mg).

T.l.c. System A (89:10:1) R_f 0.54

n.m.r. (CDCl₃) δ 2.38 (6H,s), 2.65 (4H,m), 3.16 (4H,m), 3.88 - 3.99 (6H,2xs), 6.60 (1H,d), 6.86 (1H,d), 7.26-7.43 (5H,m), 7.68-7.90 (5H,m).

From a solution of sodium carbonate (111mg) in water (5ml), followed by tetrakis(triphenylphosphine)palladium (0) (24mg) added to a mixture of 3-(4-bromophenyl)-1-methyl-1H-pyrazole (124mg) and Intermediate 7 (200mg) in DME (10ml).

5

Example 4

N-[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]-4'-(2,4-dimethyl-5-oxazolyl)[1,1'-biphenyl]-4-carboxamide

10 A mixture of Intermediate 11 (140mg), Intermediate 5 (205mg), sodium carbonate (194mg) and tetrakis(triphenylphosphine)palladium (0) (13mg) in 1:1 aqueous DME (20ml) was heated to reflux for 18h under nitrogen. Silica gel (~5g) was added, and the mixture evaporated. The residue was purified by FCC eluting with System A (200:8:1) to give the title compound as a yellow foam (151mg).

T.l.c. System A (100:8:1) Rf 0.39

15 Assay Found: C,70.2; H,6.35; N,10.7;
C₃₀H₃₂N₄O₃.H₂O requires C,70.0; H,6.65; N,10.85%

Similarly prepared were:-

20 Example 5

N-[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(2-methyl-4-thiazolyl)[1,1'-biphenyl]-4-carboxamide as a beige solid (54mg).

T.l.c. System A (100:8:1) Rf 0.36

25 n.m.r. (CDCl₃) δ 2.35 (6H,2xs), 2.64 (4H,m), 2.80 (3H,s), 3.15 (4H,m), 3.89 (3H,s), 6.87 (1H,d), 7.20-7.38 (3H,m), 7.48 (2H, 1/2 AA'BB'), 7.76-8.00 (5H,m).

From a mixture of Intermediate 5 (0.24g), Intermediate 13 (0.174g), sodium carbonate (0.227g) and tetrakis(triphenylphosphine)palladium (0) (15mg) in water (10ml) and DME (10ml).

30 Example 6

N-[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(2-oxazolyl)[1,1'-biphenyl]-4-carboxamide as a pale yellow foam (145mg).

T.l.c. System A (100:8:1) Rf 0.28

Assay Found: C,70.4; H,6.25; N,10.8;

35 C₂₉H₃₀N₄O₃.0.75H₂O requires: C,70.2; H,6.4; N,11.3%

From a mixture of Intermediate 5 (150mg) and Intermediate 16 (97mg) in 1:1

aqueous DME (20ml) containing sodium carbonate (142mg) and tetrakis(triphenylphosphine)palladium (0) (10mg).

Example 7

5 N-[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-2-oxazolyl)[1,1'-biphenyl]-4-carboxamide as an off-white foam (195mg)

T.l.c. System A (100:8:1) R_f = 0.39

n.m.r. (CDCl₃) δ 2.32-2.44 (9H, 2xs), 2.63 (4H,m), 3.15 (4H,m), 3.89 (3H,s), 6.86 (2H,m), 7.22-7.34 (3H,m), 7.46 (2H, 1/2 AA'BB'), 7.81-7.98 (5H,m).

10 From a mixture of Intermediate 10 (200mg) and Intermediate 5 (293mg) in 1:1 aqueous DME (20ml) containing sodium carbonate (277mg) and tetrakis(triphenylphosphine)palladium (0) (18mg). Additional chromatography on silica gel (Merck 7729) eluting with System A (200:8:1) gave the title compound.

15 Example 8

N-[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(1,3-oxathiolan-2-yl)[1,1'-biphenyl]-4-carboxamide

A mixture of Intermediate 17 (200mg) and Intermediate 5 (285mg) in 1:1 aqueous DME (20ml) containing sodium carbonate (270mg) and
20 tetrakis(triphenylphosphine)palladium (0) (18mg) was heated at reflux for 18h under nitrogen. The mixture was allowed to cool, and silica gel (Merck 9385) was added. The mixture was evaporated to dryness and the residue purified by chromatography eluting with System A (200:8:1) to give the title compound as a yellow foam (233mg).

25 T.l.c. System A (100:8:1) R_f 0.47

n.m.r. (CDCl₃) δ 2.28 (3H,s), 2.38 (3H,s), 2.64 (4H, br.m), 3.15 (4H, br.m), 3.28 (2H,m), 3.88 (3H,s), 3.99 & 4.58 (2H, 2xm), 6.09 (1H,s), 6.87 (1H,d), 7.2-7.46 (7H,m), 7.76 (1H,br.s), 7.91 (2H, 1/2AA'BB').

30 Similarly prepared were:-

Example 9

4'-(4,5-Dihydro-2-oxazolyl)-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl[1,1'-biphenyl]-4-carboxamide as a colourless foam (154mg).

35 T.l.c. System A (100:8:1) R_f 0.40

Assay Found:

C,68.35; H,6.7; N,10.8;

C₂₉H₃₂N₄O₃.1.5H₂O requires C,68.1; H,6.9; N,10.95%
From a mixture of Intermediate 15 (150mg) and Intermediate 5 (230mg) in 1:1 aqueous DME (20ml) containing sodium carbonate (218mg) and tetrakis(triphenylphosphine)palladium (0) (14mg).

5

Example 10

(S)-4'-(4,5-Dihydro-5-methyl-2-oxazolyl)-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl[1,1'-biphenyl]-4-carboxamide as a colourless powder (80mg).

10 T.l.c. System A (100:8:1) R_f 0.32

Assay Found:

C,71.5; H,6.8; N,11.05;

C₃₀H₃₄N₄O₃. 0.25H₂O requires:

C,71.6; H,6.9; N,11.15%

From a mixture of Intermediate 19 (160mg), Intermediate 5 (775mg) and tetrakis(triphenylphosphine)palladium (0) (20mg) in 1:1 aqueous DME (20ml).

15 Trituration with ether gave the title compound.

The following examples illustrate pharmaceutical formulations according to the invention. The term "active ingredient" is used herein to represent a compound of formula (I).

20

Pharmaceutical Example 1

Oral Tablet A

	Active Ingredient	700mg
25	Sodium starch glycollate	10mg
	Microcrystalline cellulose	50mg
	Magnesium stearate	4mg

30

Sieve the active ingredient and microcrystalline cellulose through a 40 mesh screen and blend in a appropriate blender. Sieve the sodium starch glycollate and magnesium stearate through a 60 mesh screen, add to the powder blend and blend until homogeneous. Compress with appropriate punches in an automatic tablet press. The tablets may be coated with a thin polymer coat applied by the film coating techniques well known to those skilled in the art. Pigments may be

35

incorporated in the film coat.

Pharmaceutical Example 2Oral Tablet B

5	Active Ingredient	500mg
	Lactose	100mg
	Maize Starch	50mg
	Polyvinyl pyrrolidone	3mg
	Sodium starch glycollate	10mg
10	Magnesium stearate	4mg
	Tablet Weight	667mg

15 Sieve the active ingredient, lactose and maize starch through a 40 mesh screen and blend the powders in a suitable blender. Make an aqueous solution of the polyvinyl pyrrolidone (5 - 10% w/v). Add this solution to the blended powders and mix until granulated; pass the granulate through a 12 mesh screen and dry the granules in a suitable oven or fluid bed dryer. Sieve the remaining components through a 60 mesh screen and blend them with the dried granules. Compress, 20 using appropriate punches, on an automatic tablet press.

The tablets may be coated with a thin polymer coat applied by film coating techniques well known to those skilled in art. Pigments may be incorporated in the film coat.

25

Pharmaceutical Example 3Inhalation Cartridge

	Active Ingredient	1mg
30	Lactose	24mg

Blend active ingredient, particle size reduced to a very fine particle size (weight mean diameter ca. 5 μ m) with the lactose in a suitable powder blender and fill the powder blender into No. 3 hard gelatin capsules.

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The contents of the cartridges may be administered using a powder inhaler.

Pharmaceutical Example 4Injection Formulation

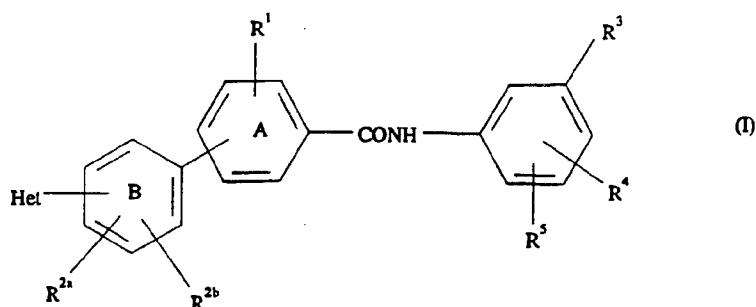
		% w/v
5	Active ingredient	1.00
	Water for injections B.P. to	100.00

10 Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability and/or to facilitate solution of the active ingredient using dilute acid or alkali or by the addition of suitable buffer salts. Antioxidants and metal chelating salts may also be included.

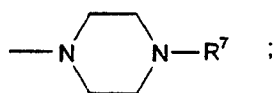
15 The solution is prepared, clarified and filled into appropriate sized ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen.

CLAIMS

1. A compound of formula (I) :-

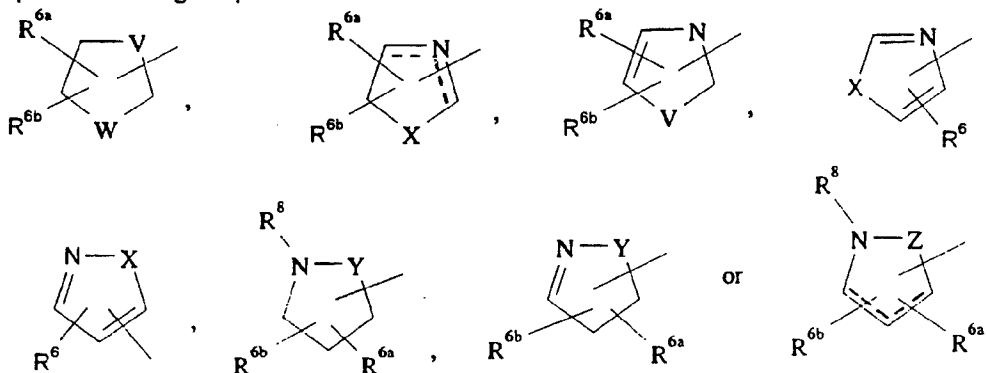


- or a salt or solvate (e.g. hydrate) thereof, in which
 R¹ represents a hydrogen atom, a halogen atom, C₁₋₆alkyl or C₁₋₆alkoxy;
 R^{2a} and R^{2b}, which may be the same or different, each independently represents
 a hydrogen atom, a halogen atom, C₁₋₆alkoxy, hydroxy or C₁₋₆alkyl;
 R³ represents the group



R⁴ and R⁵, which may be the same or different, each independently represents a
 hydrogen atom, a halogen atom, hydroxy, C₁₋₆alkoxy or C₁₋₆alkyl;

Het represents a group selected from



R⁶ represents a hydrogen atom, -NR⁹R¹⁰ or C₁₋₆alkyl optionally substituted by

one or two substituents selected from C₁₋₆alkoxy, hydroxy and -OCOR¹¹;

R^{6a} and R^{6b}, which may be the same or different, each independently represent a hydrogen atom, a hydroxy group or C₁₋₆alkyl optionally substituted by one or two substituents selected from C₁₋₆alkoxy and hydroxy;

R⁷, R⁸ and R⁹, which may be the same or different, each independently represent a hydrogen atom or a C₁₋₆alkyl group;

R¹⁰ represents a hydrogen atom C₁₋₆alkyl, COR¹¹, benzoyl or -SO₂R¹¹;

R¹¹ represents C₁₋₆alkyl or phenyl;

V and W, which may be the same or different, each independently represent an oxygen or a sulphur atom;

X represents an oxygen atom or the group NR⁸ or S(O)_k;

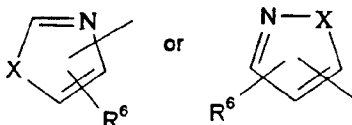
Y represents an oxygen atom or the group NR⁸ or SO₂;

Z represents a sulphur atom or the group NR⁸;

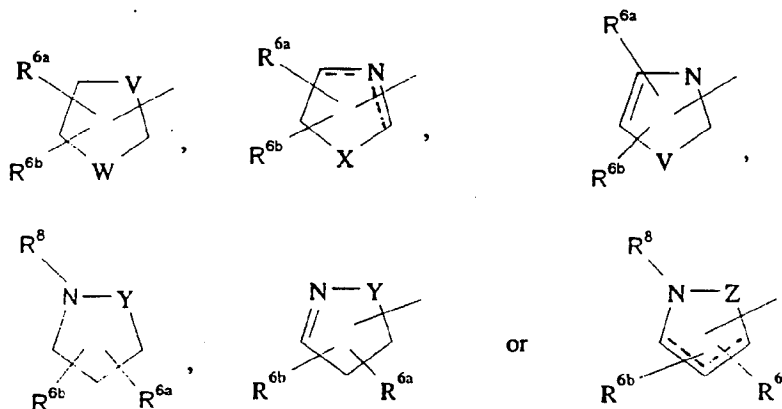
k represents zero, 1 or 2; and

the dotted line represents a double bond present in either of the positions indicated.

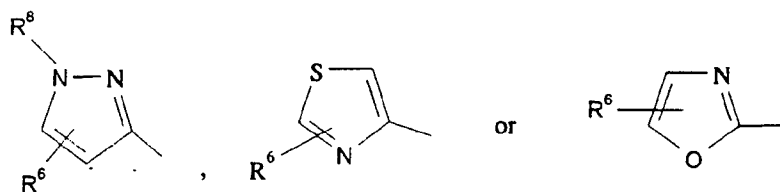
2. A compound as claimed in Claim 1 wherein Het represents a group



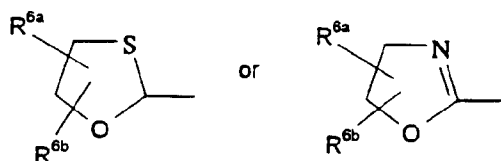
3. A compound as claimed in Claim 1 wherein Het represents a group



4. A compound as claimed in Claim 2 wherein Het represents a group



5. A compound as claimed in Claim 3 wherein Het represents a group



6. A compound as claimed in any preceding Claim wherein the group Het on the phenyl ring B is attached at the position para to the phenyl ring A.

7. A compound as claimed in any preceding Claim wherein R^1 represents a hydrogen atom or C_{1-6} alkyl.

8. A compound as claimed in any preceding Claim wherein one of R^{2a} and R^{2b} represents a hydrogen atom and the other of R^{2a} and R^{2b} represents a hydrogen atom or C_{1-6} alkyl and is attached to the phenyl ring B at a position ortho to the phenyl ring A.

9. A compound as claimed in any preceding Claim wherein R^4 is attached at the para position relative to the amide linkage.

10. A compound as claimed in any preceding Claim wherein R^4 represents a halogen atom and the other of R^{2a} and R^{2b} or a hydroxy or C_{1-6} alkoxy group.

11. A compound as claimed in any preceding Claim wherein R^5 represents a hydrogen atom.

12. A compound as claimed in any one of Claims 1, 2, 4 and 6 to 11 wherein R^{6a} and R^{6b} each independently represents a hydrogen atom or C_{1-6} alkyl optionally

substituted by C₁₋₆alkoxy.

13. A compound as claimed in any one of Claims 1, 3 and 5-11 wherein R⁶ represents a hydrogen atom or C₁₋₆ alkyl optionally substituted by C₁₋₆alkoxy.

14. A compound as claimed in any preceding Claim wherein R⁷ represents C₁₋₃alkyl.

15. A compound selected from:

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2-methyl-4'-(1-methyl-1H-pyrazol-3-yl)[1,1'-biphenyl]-4-carboxamide;

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(2-methyl-4-thiazolyl)[1,1'-biphenyl]-4-carboxamide;

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(2-oxazolyl)[1,1'-biphenyl]-4-carboxamide;

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-2-oxazolyl)[1,1'-biphenyl]-4-carboxamide;

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(1,3-oxathiolan-2-yl)[1,1'-biphenyl]-4-carboxamide;

4'-(4,5-dihydro-2-oxazolyl)-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl[1,1'-biphenyl]-4-carboxamide;

and salts and solvates thereof.

16. A compound as claimed in any preceding Claim for use in therapy.

17. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 15 and a pharmaceutically acceptable carrier.

18. A compound as claimed in any one of Claims 1 to 15 and an antidepressant

agent in the presence of each other in the human or non-human animal body for use in the treatment of depression.

19. A compound as claimed in any one of Claims 1 to 15 and an antiparkinsonian agent in the presence of each other in the human or non-human animal body for use in the treatment of Parkinson's disease, dementia in Parkinson's disease, neuroleptic - induced parkinsonism or tardive dyskinesias.

20. A method for the treatment of

(i) depression; or

(ii) CNS disorders, selected from mood disorders such as seasonal affective disorder and dysthymia; anxiety disorders such as generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders such as dementia, amnesic disorders and age-associated memory impairment; and disorders of eating behaviour such as anorexia nervosa and bulimia nervosa; or

(iii) a disease selected from Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias; or

(iv) endocrine disorders, vasospasm, hypertension, disorders of the gastrointestinal tract where changes in motility and secretion are involved, and sexual dysfunction; which comprises administering to a patient in need of such treatment an effective amount of a compound of formula (I) as defined in Claim 1 or a physiologically acceptable salt or solvate thereof.

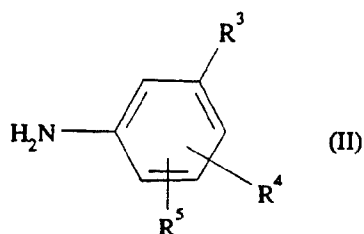
21. A method for the treatment of depression which comprises administering to a patient in need of such treatment an effective amount of a compound of formula (I) as defined in Claim 1 or a physiologically acceptable salt or solvate thereof and an antidepressant agent.

22. A method for the treatment of Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias which comprises administering to a patient in need of such treatment an effective amount of a compound of formula (I) as defined in Claim 1 or a physiologically acceptable salt or solvate thereof and an antiparkinsonian agent.

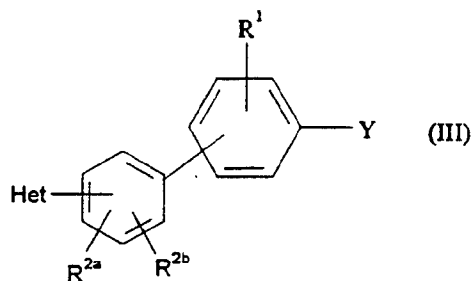
23. A process for the preparation of a compound as claimed in any one of Claims

1 to 15 which process comprises:

(1) reacting an aniline (II)



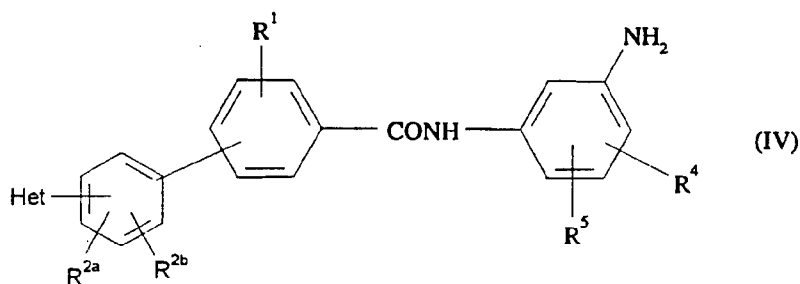
5 wherein R³, R⁴ and R⁵ are as defined in general formula (I), with a halophenyl compound (III)



10 wherein Y represents a halogen atom or the group -OSO₂CF₃, and Het, R¹, R^{2a} and R^{2b} are as defined in general formula (I), in the presence of carbon monoxide and a catalyst, followed, if necessary, by the removal of any protecting group where present; or

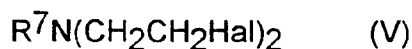
(2) treating compound of formula (IV)

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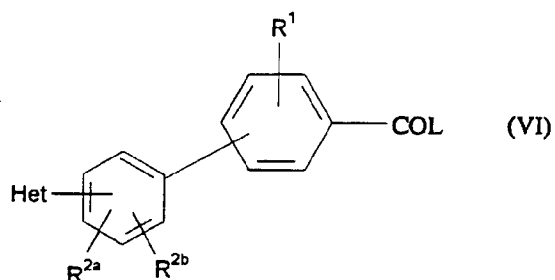
with an amine dihalide of formula (V)

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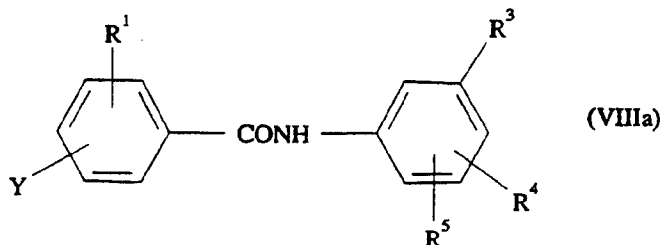
wherein Hal is a chlorine, bromine or iodine atom, followed, if necessary, by the removal of any protecting group where present; or

(3) reacting an aniline of formula (II) with an activated carboxylic acid derivative of formula (VI)

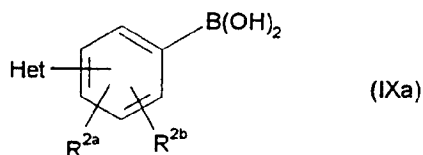


wherein L is a leaving group, followed, if necessary, by the removal of any protecting group where present; or

(4a) treating a compound of formula (VIIIa)



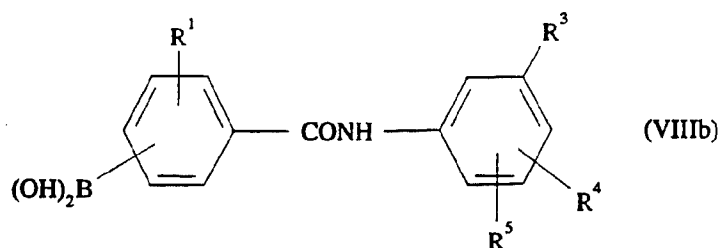
wherein Y represents a bromine or iodine atom or the group $-\text{OSO}_2\text{CF}_3$, with a compound of formula (IXa)



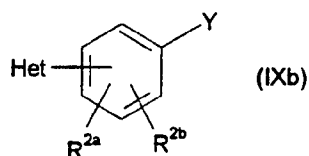
or an ester, an anhydride or a salt thereof, or

(4b) treating a compound of formula (VIIIb)

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or an ester, an anhydride or a salt thereof, with a compound of formula (IXb)



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wherein Y represents a bromine or iodine atom or the group -OSO₂CF₃, followed, if necessary, by the removal of any protecting group where present;

and when the compound of general formula (I) is obtained as a mixture of enantiomers, optionally resolving the mixture to obtain the desired enantiomer;
 10 and/or, if desired, converting the resulting compounds of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate thereof.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D231/12 C07D233/64 C07D263/32 C07D277/30 C07D327/04
C07D263/10 A61K31/42 A61K31/425 A61K31/415 A61K31/39

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ARCHIV DER PHARMAZIE vol. 315, no. 2 , February 1982 , WEINHEIM pages 97 - 103 E.S. CHARLES ET AL 'Synthesis of substituted benzamides, benzimidazoles and benzoxazines as potential anthelmintic and antimicrobial agents' see the whole document -----	1,16,17
P,X	EP,A,0 533 268 (GLAXO GROUP LIMITED) 24 March 1993 see claims -----	1-23

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 "&" document member of the same patent family

Date of the actual completion of the international search

18 March 1994

Date of mailing of the international search report

30.03.94

Name and mailing address of the ISA

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Henry, J

Information on patent family members

PCT/EP 93/03708

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 93/03708

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 20-22 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.